PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
C07D 453/02, A61K 31/435	A1	WO 92/12151
		(43) International Publication Date: 23 July 1992 (23.07.92)

(21) International Application Number: PCT/US91/08836

(22) International Filing Date: 4 December 1991 (04.12.91)

(30) Priority data:
639,644 10 January 1991 (10.01.91) US

(60) Parent Application or Grant
(63) Related by Continuation
US 639,644 (CON)
Filed on 10 January 1991 (10.01.91)

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 236 East 45nd Street, New York, NY 10017 (US).

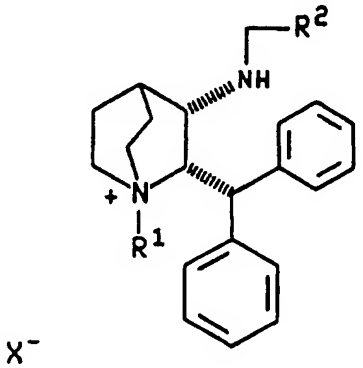
(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : LOWE, John, A., III [US/US]; 28 Coveside Lane, Stonington, New London, CT 06378 (US).

(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), NO, SE (European patent), US.

Published
With international search report.

(54) Title: N-ALKYL QUINUCLIDINIUM SALTS AS SUBSTANCE P ANTAGONISTS



(I)

(57) Abstract

The present invention relates to novel N-alkyl quinuclidinium salts, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment and prevention inflammatory and gastrointestinal disorders, as well as several other disorders. The N-alkyl quinuclidinium salts of this invention have formula (I), wherein R^1, R^2, and X^- are as defined below.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland			SE	Sweden
CI	Côte d'Ivoire	KR	Republic of Korea	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
DE	Germany	LU	Luxembourg	TG	Togo
DK	Denmark	MC	Monaco	US	United States of America

N-ALKYL QUINUCLIDINIUM SALTS AS SUBSTANCE P ANTAGONISTS

Background of the Invention

The present invention relates to novel N-alkyl quinuclidinium salts, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment and prevention inflammatory and gastrointestinal disorders, as well as several other disorders. The pharmaceutically active compounds of this invention are substance P antagonists.

Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being named because of their prompt stimulatory action on smooth muscle tissue. More specifically, substance P is a pharmacologically active neuropeptide that is produced in mammals (having originally been isolated from gut) and possesses a characteristic amino acid sequence that is illustrated by D. F. Veber et al. in U.S. Patent No. 4,680,283. The wide involvement of substance P and other tachykinins in the pathophysiology of numerous diseases has been amply demonstrated in the art. For instance, substance P has recently been shown to be involved in the transmission of pain or migraine (see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, 25, 1009 (1982)), as well as in central nervous system disorders such as anxiety and schizophrenia, in respiratory and inflammatory diseases such as asthma and rheumatoid arthritis, respectively, in rheumatic diseases such as fibrositis, and in gastrointestinal disorders and diseases of the GI tract such as ulcerative colitis and Crohn's disease, etc. (see D. Regoli in "Trends in Cluster Headache," edited by F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, pp. 85-95 (1987)).

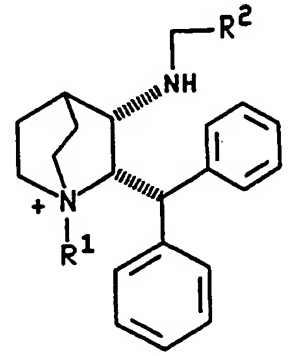
Quinuclidine derivatives and related compounds that exhibit activity as substance P receptor antagonists are referred to in PCT Patent Application PCT/US 89/05338, filed November 20, 1989 and United States Patent Application Serial No. 557,442, filed July 23, 1990, both of which are assigned in common with the present application. Similar compounds are referred to in the PCT patent applications entitled "3-Amino-2-Aryl Quinuclidines" and "Quinuclidine Derivatives" and filed on April 25, 1991 and May 15, 1991, respectively. These applications are also assigned in common with the present application.

Piperidine derivatives and related heterocyclic nitrogen containing compounds that are useful as substance P antagonists are referred to in United States Patent Application Serial No. 619,361, filed November 28, 1990 and United States Patent

Application Serial No. 590,423, filed September 28, 1990, both of which are assigned in common with the present application.

Summary of the Invention

The present invention relates to compounds of the formula



(I)

wherein R^1 is $(C_1\text{-}C_4)$alkyl, allyl, phenyl-$(C_1\text{-}C_6)$alkyl, HOOC-$(C_1\text{-}C_{10})$alkyl or $(C_1\text{-}C_4)$alkoxy-OOC-$(C_1\text{-}C_{10})$alkyl; R^2 is selected from the group consisting of phenyl, thienyl, furyl and pyridyl, each of the foregoing R^2 groups being optionally substituted with from one to three substituents independently selected from the group consisting of cyano, nitro, amino, N-mono-$(C_1\text{-}C_3)$alkylamino, fluorine, chlorine, bromine, trifluoromethyl, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, allyoxy, $(C_1\text{-}C_3)$alkoxy-carbonyl, carboxamido and N,N-di-$(C_1\text{-}C_3)$alkyl-carboxamido; and X^- is a pharmaceutically acceptable counterion, (e.g., chloride, bromide, fluoride, iodide, mesylate, tosylate or trifluoromethanesulfonate).

Examples of pharmaceutically acceptable counterions are halides (e.g., fluoride, chloride, bromide or iodide), $(C_1\text{-}C_3)$alkyl-mono or di-carboxylates, mesylate, tosylate, arylcarboxylates, $(C_1\text{-}C_3)$alkylsulfonates wherein the alkyl moiety may optionally be substituted with one or more fluorine atoms, arylsulfonates, citrate, maleate, fumarate, lactate, malate, sulfates, phosphates, nitrates, tartrate, saccharate and pamoate.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

Preferred compounds of the formula I are those wherein R^2 is 2-methoxyphenyl.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), colitis, pain, allergies

such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, peripheral neuropathy, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), colitis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, peripheral neuropathy, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition.

The present invention also relates to a pharmaceutical composition for antagonizing the effects of substance P in a mammal, including a human, comprising a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of antagonizing the effects of substance P in a mammal, including a human, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising a substance P antagonizing amount of a compound of the

formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), colitis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, peripheral neuropathy, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), colitis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, peripheral neuropathy, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated

neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder.

The compounds of the formula I have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I, and mixtures thereof.

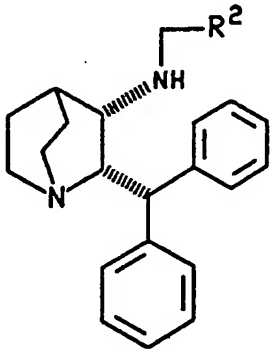
The optically active compounds of formula I are additionally useful as intermediate in the synthesis of the corresponding racemic mixtures and opposite enantiomers.

Formula I above includes compounds identical to those depicted but for the fact that one or more hydrogen or carbon atoms are replaced by radioactive isotopes thereof, (e.g., tritium, carbon-14 or nitrogen-15 isotopes thereof). Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and <u>in vivo</u> binding

studies, while specific applications in the diagnostic area include studies of the substance P receptor in humans in in vivo binding in the relevant tissues for inflammation, e.g. immune-type cells or cells that are directly involved in inflammatory bowel disorders and the like.

Detailed Description of the Invention

Compounds of the formula I may be prepared by reacting the corresponding compound of the formula



(II)

wherein R^2 is defined as above, with a compound of the formula R^1X, wherein R_1 is defined as above and X is chloro, fluoro, bromo, iodo, tosyloxy, mesyloxy, or trifluoromethanesulfonyloxy. The reaction is generally carried out in a polar solvent such as ethanol, acetone, dimethylformamide or tetrahydrofuran, at a temperature from about 0°C to about 150°C, preferably at about the reflux temperature of the solvent.

Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e. about 1 atmosphere, is preferred as a matter of convenience.

The novel compounds of the formula I and the pharmaceutically acceptable salts thereof are useful as substance P antagonists, i.e., they possess the ability to antagonize the effects of substance P at its receptor site in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the Formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert such

salt to an alternate, pharmaceutically acceptable salt by standard ion exchange methods known to those skilled in the art. In additional, the acid addition salts of the compounds of this invention are readily prepared by treating the appropriate compound of formula I with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

The compounds of Formula I and their pharmaceutically acceptable salts exhibit substance P receptor-binding activity and therefore are of value in the treatment and prevention of a wide variety of clinical conditions the treatment or prevention of which are effected or facilitated by a decrease in substance P mediated neurotransmission. Such conditions include inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), colitis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, peripheral neuropathy, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

The compounds of the formula I and the pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 5.0 mg up to about 1500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be

employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous

solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The activity of the compounds of the present invention as substance P antagonists is determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing radioactive ligands to visualize the tachykinin receptors by means of auto-radiography. The substance P antagonizing activity of the herein described compounds may be evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic IC_{50} values for each compound tested.

In this procedure, bovine caudate tissue is removed from a -70°C freezer and homogenized in 50 volumes (w./v.) of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty- minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 40 g/ml of bacitracin, 4μg/ml of leupeptin, 2μg of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100 μl of the test compound made up to a concentration of 1 μM, followed by the addition of 100 μl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 μl of the tissue preparation produced as described above. The final volume is thus 1.0 ml,

and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC_{50} values are calculated by using standard statistical methods.

The present invention is illustrated by the following example. It will be understood, however, that the invention is not limited to the specific details of this example.

EXAMPLE 1

(2S,3S)-cis-1-Methyl-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-aza-bicyclo[2.2.2]octan-3-amine iodide: To a 50 mL round-bottomed flask equipped with condenser and N_2 inlet were added 500 mg (1.21 mmol) (2S,3S)-cis-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine and 6 mL ethanol. The solution was heated to near boiling, and 207 mg (1.46 mmol) methyl iodide was added. Heating was continued for 10 min, then the solution was cooled to afford a precipitate, which was filtered and dried. The resulting solid gave mp 239-244°C, 328 mg (49% yield).

^{1}H-NMR (δ, $CDCl_3$): 1.8-2.0 (m, 2H), 2.1-2.3 (m, 2H), 2.47 (s, 3H), 2.59 (m, 1H), 3.04 (dd, J=13,84, 2H) (m, 1H), 3.50 (m, 1H), 3.63 (s, 3H), 3.67 (s, 1H), 3.95 (m, 1H), 4.12 (m, 1H), 4.46 (d, J=11.5, 1H), 5.42 (dd, J=6.5, 11.5, 1H), 6.33, 6.68, and 7.07-7.2 (multiplets, 14H), 7.7-7.9 (broad m, 2H).

^{13}C-NMR (δ, $CDCl_3$): 20.0, 22.4, 23,8, 46.1, 49.4, 53.9, 54.6, 55.3, 55.6, 61.2, 71.5, 110.2, 120.4, 126.9, 127.2, 127.9, 128.5, 129.6, 141.7, 143.5, 157.1.

Mass Spec. (%): 426 (1, parent), 259 (31), 245 (46), 142 (45), 121 (100), 91 (62).

The title compounds of Examples 2-8 were prepared by a procedure similar to that of Example 1.

EXAMPLE 2

(2S,3S)-cis-1-(4-Carbethoxybutyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine iodide:

Prepared in 13% yield, m.p. 85°C.

Mass Spec.: 541 (1, parent), 373 (89), 359 (56), 121 (100), 91 (45).

EXAMPLE 3

(2S,3S)-cis-1-(4-Carboethoxyphenylmethyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine iodide:

Prepared in 13% yield, m.p. 140-145°C.

Anal. Calc'd for $C_{38}H_{43}N_2O_3I \cdot 1/3H_2O$: C 64.40, H 6.21, N 3.95. Found: C 64.05, H 6.16, N 3.88.

EXAMPLE 4

(2S,3S)-cis-1-(5-Carbomethoxypentyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine triflate:

Prepared (using acetonitrile instead of ethanol as solvent) in 5% yield, as an oil.

Anal. Calc'd for $C_{36}H_{45}N_2O_6SF_3 \cdot HCl \cdot 1/2H_2O$: C 57.32, H 6.55, N 3.71. Found: C 57.29, H 6.48, N 3.68. Found: C 57.29, H 6.48, N 3.68.

EXAMPLE 5

(2S,3S)-cis-1-(5-Carboxypentyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine triflate:

Prepared by hydrolysis of the above compound with potassium hydroxide in ethanol.

High Res. Mass Spec: Calc'd for $C_{34}H_{43}N_2O_3$: 527.3278. Found: 527.3268.

EXAMPLE 6

(2S,3S)-cis-1-Allyl-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine bromide:

Prepared in 58% yield, m.p. 150-160°C.

Anal. Calc'd for $C_{31}H_{37}N_2OBr \cdot 1.25H_2O$: C 66.96, H 7.16, N 5.04. Found: C 66.95, H 7.06, N 4.97.

EXAMPLE 7

(2S,3S)-cis-1-Benzyl-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine bromide:

Prepared in 53% yield, m.p. 206-208°C.

Anal. Calc'd for $C_{35}H_{39}N_2OBr \bullet H_2O$: C 69.87, H 6.87, N 4.66. Found: C 69.48, H 6.84, N 4.52.

EXAMPLE 8

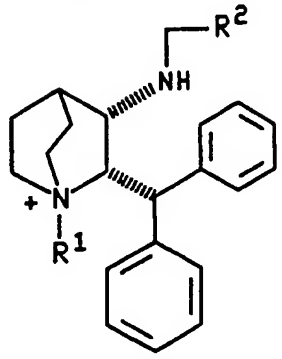
(2S,3S)-cis-1-(Carboethyoxymethyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine bromide:

Prepared in 17% yield, m.p. 125-135°C.

Anal. Calc'd for $C_{32}H_{39}N_2O_3Br \bullet H_2O$: C 64.32, H 6.92, N 4.69. Found: C 64.14, H 6.88, N 4.62.

CLAIMS

1. A compound of the formula



(I)

wherein R^1 is $(C_1\text{-}C_4)$alkyl, allyl, phenyl-$(C_1\text{-}C_6)$alkyl, HOOC-$(C_1\text{-}C_{10})$alkyl or $(C_1\text{-}C_4)$alkoxy-OOC-$(C_1\text{-}C_{10})$alkyl; R^2 is selected from the group consisting of phenyl, thienyl, furyl and pyridyl, each of the foregoing R^2 groups being optionally substituted with from one to three substituents independently selected from the group consisting of cyano, nitro, amino, N-mono-$(C_1\text{-}C_3)$alkylamino, fluorine, chlorine, bromine, trifluoromethyl, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, allyoxy, $(C_1\text{-}C_3)$alkoxy-carbonyl, carboxamido and N,N-di-$(C_1\text{-}C_3)$alkyl-carboxamido; and X^- is a pharmaceutically acceptable counterion, or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R_2 is 2-methoxyphenyl.

3. A compound according to claim 2 wherein R_1 is methyl.

4. A compound according to claim 3 wherein X^- is iodide.

5. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases, arthritis, colitis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, peripheral neuropathy, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound according to claim 1 effective in preventing or treating such condition and a pharmaceutically acceptable carrier.

6. A method of treating or preventing a condition selected from the group consisting of inflammatory diseases arthritis, colitis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and

collagen diseases, reflex sympathetic dystrophy, peripheral neuropathy, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in preventing or treating such condition.

7. A pharmaceutical composition for antagonizing the effects of substance P in a mammal, comprising a substance P antagonizing effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

8. A method of antagonizing the effects of substance P in a mammal, comprising administering to said mammal a substance P antagonizing effective amount of a compound according to claim 1.

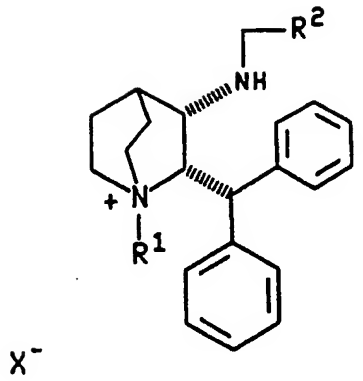
9. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

10. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

11. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

12. A method of treating or preventing a condition in mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in treating or preventing such condition.

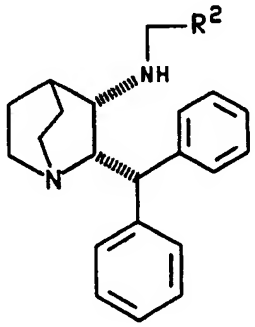
13. A process for preparing a compound of the formula



(I)

wherein R^1 is (C_1-C_4)alkyl, allyl, phenyl-(C_1-C_6)alkyl, HOOC-(C_1-C_{10})alkyl or (C_1-C_4)alkoxy-OOC-(C_1-C_{10})alkyl; R^2 is selected from the group consisting of phenyl, thienyl, furyl and pyridyl, each of the foregoing R^2 groups being optionally substituted with from one to three substituents independently selected from the group consisting of cyano, nitro, amino, N-mono-(C_1-C_3)alkylamino, fluorine, chlorine, bromine, trifluoromethyl, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, allyoxy, (C_1-C_3)alkoxy-carbonyl, carboxamido and N,N-di-(C_1-C_3)alkyl-carboxamido; and X^- is a pharmaceutically acceptable counterion;

comprising reacting a compound of the formula



(II)

wherein R^2 is defined as above, with a compound of the formula R^1X, wherein R^1 is defined as above and X is chloro, fluoro, bromo, iodo, tosyloxy, mesyloxy or trifluoromethanesulfonyl.

14. A process according to claim 13, wherein the compound of formula I prepared by said process is a compound wherein R^2 is 2-methoxyphenyl.

15. A process according to claim 13, wherein the compound of formula I prepared by said process is a compound wherein R^1 is methyl.

16. A process according to claim 13 wherein the compound of formula I prepared by said process is a compound wherein X^- is iodide.

17. A process according to claim 13, wherein the compound of formula I prepared by said process is a compound wherein R^1 is selected from carboethoxybutyl, carboethoxyphenylmethyl, carbomethoxypenyl, carboxypentyl, benzyl, allyl, and carboethoxymethyl.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/08836

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 453/02, A 61 K 31/435

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO, A1, 9005525 (PFIZER INC.) 31 May 1990, see the whole document	1-5,7,9, 11,13-17
X	WO, A1, 9005729 (PFIZER INC.) 31 May 1990, see the whole document	1-5,7,9, 11,13-17
A	EP, A2, 0404737 (ISTITUTO DE ANGELI S.P.A.) 27 December 1990, see the whole document	1-5,7,9, 11,13-17

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1st April 1992	24.04.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	D. Kraus
	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A1, 0159059 (LABORATORI GUIDOTTI S.P.A.) 23 October 1985, see the whole document	1-5,7,9, 11,13-17

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 6,8,* because they relate to subject matter not required to be searched by this Authority, namely:

*10,12

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods [PCT Rule 39.1 (iv)].

2. [ ] Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 91/08836

SA 54661

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/02/92
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A1- 9005525	31/05/90	CA-A-	2003441	23/05/90
		EP-A-	0409931	30/01/91
		WO-A-	90/05729	31/05/90
WO-A1- 9005729	31/05/90	CA-A-	2003441	23/05/90
		EP-A-	0409931	30/01/91
		WO-A-	90/05525	31/05/90
EP-A2- 0404737	27/12/90	AU-D-	5764990	03/01/91
		CA-A-	2019251	20/12/90
		JP-A-	3031279	12/02/91
EP-A1- 0159059	23/10/85	DE-A-	3509460	19/09/85
		JP-A-	60209521	22/10/85
		US-A-	4603132	29/07/86